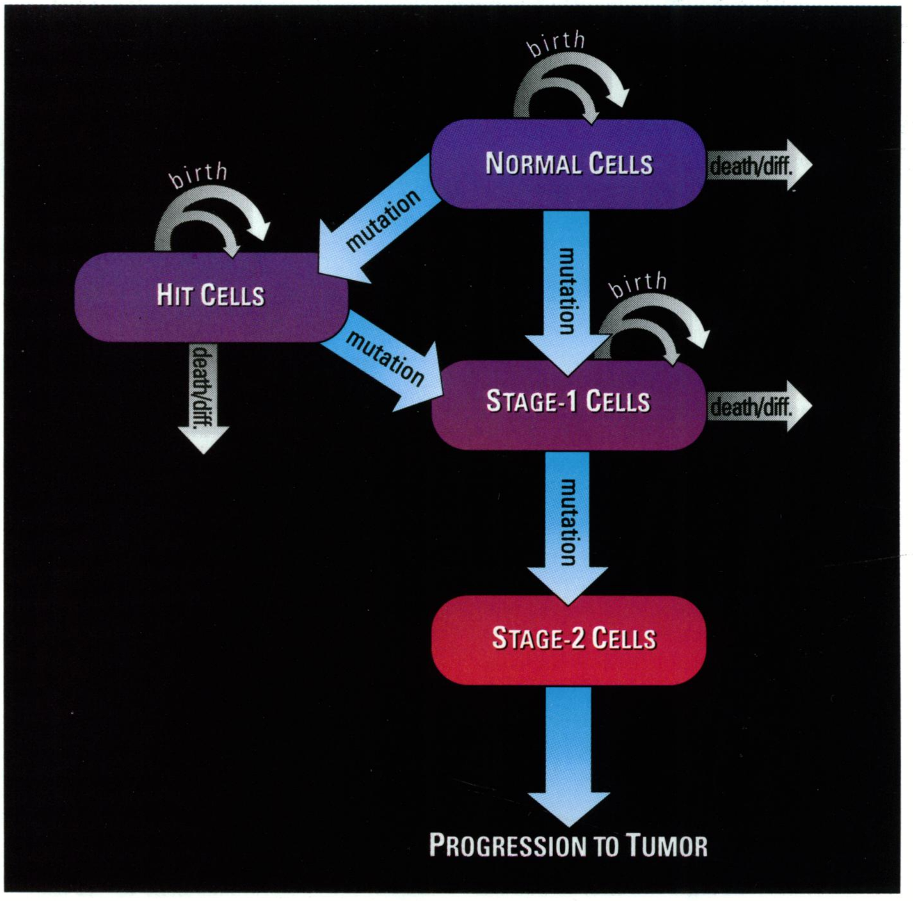
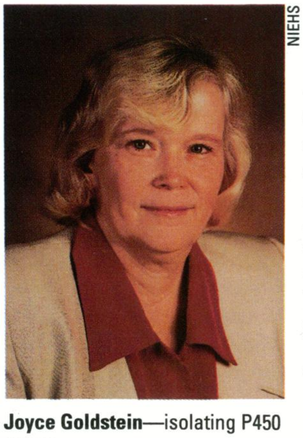
NIEHS investigators have developed sensitive assays to detect susceptibility to carcinogens in cigarette smoke, foods, industrial by-products, and environmental pollution. Based on tests of more than 1000 individuals for these susceptibility genes, the frequency of the at-risk genotypes vary significantly among Asians, Caucasians, and African-Americans. Such variation suggests that some of the differences in cancer incidence among ethnic groups may be due to genetic differences as well as exposure differences.

In collaboration with Jack Taylor of the NIEHS Epidemiology Branch, LBRA is testing the effect of certain cancer susceptibility genes in studies of bladder cancer, lung cancer, and liver cancer. Individuals who carry the at-risk genotype for glutathione transferase μ, an enzyme that detoxifies constituents of cigarette smoke, suffer a 70% increased risk of bladder cancer. In ongoing studies with researchers at the National Cancer Institute, Columbia University, University of North Carolina, and University of Keele, England, NIEHS is exploring how genetic variability in the metabolism of carcinogens affects risk for cancer of the bladder, lung, liver, stomach, colon, head, and neck.

The cytochrome P450 enzymes catalyze the oxidation of drugs, carcinogens, and other xenobiotics. Joyce Goldstein's group in LBRA is looking for genetic defects in these enzymes that affect the ability of humans to metabolize chemical agents. Population studies have shown that some people are poor metabolizers of the drug *S*-mephenytoin, and defective metabolism is inherited. Metabolism of other drugs, including barbiturates, the antimalarials, and the antiulcer drug omeprazole, may be mediated by the same enzyme. Goldstein's group has isolated two new genes in the P450 subfamily. These studies use conventional cloning techniques and polymerase chain reaction to identify genetic differences in genes from poor or extensive metabolizers of the drugs. The ability of proteins coded by these genes to metabolize drugs and chemicals is being studied by Burhan Ghanayem of LBRA.



A clonal two-path/two-stage model of carcinogenesis is being developed by members of the LQCB.



Joyce Goldstein—isolating P450 genes

Laboratory of Quantitative and Computational Biology

High-speed computing, the improved ability to collect a broad range of data at the biochemical and molecular levels, and recent advances in mathematics and statistics have significantly enhanced the utility of mathematical modeling in describing and studying environmental risks. The emergence of these new technologies requires a multidisciplinary approach in the quantitative sciences and creates the need for research teams in quantitative and computational areas. To address this need, NIEHS is creating a new laboratory, the Laboratory of Quantitative and Computational Biology (LQCB). The primary responsibility of LQCB is to investigate the application of mathematics, statistics, computational chemistry, electrical engineering, and computer science to the understanding of human health risks from exposure to environmental agents. LQCB will initially combine scientists from three research groups at NIEHS: a group developing new methodology and applying existing methodology to the application of quantum and statistical mechanics in environmental health, a group focusing on research in mathematical modeling aimed at developing new methodologies for risk estimation, and the NIEHS Scientific Computing Laboratory, whose primary purpose is computational support and direction for intramural research at NIEHS. In addition to these scientists, the LQCB plans to add expertise in a variety of related fields, including artificial intelligence and virtual reality. LQCB will be able to model biological mechanisms at all levels of complexity from molecular to demographic. The collaboration of LQCB and other NIEHS branches will lead to more efficient use of NIEHS resources through improved experimental design and the formal use of data from multiple sources. Current research and short-term research plans for the LQCB can be divided into seven broad areas: carcinogenic modeling, molecular modeling, biochemical and pharmacological modeling, modeling noncarcinogenic endpoints, computer science, artificial intelligence, and risk communication. Christopher Portier will be acting chief of this new laboratory.

Challenging a Dioxin Hypothesis

Dioxin is believed by many to be one of the most potent carcinogens in the environment. Emerging information at the molecular level concerning the mechanism of